Effect of Liraglutide on Cardiovascular Events in Patients With Type 2 Diabetes Mellitus and Polyvascular Disease

Results of the LEADER Trial

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The presence of polyvascular disease, defined as atherosclerosis involving >1 distinct vascular territory, is a strong, independent predictor of cardiovascular events.[1–4] In the LEADER trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results),[5] the human glucagon-like peptide 1 analog liraglutide reduced cardiovascular events in patients with type 2 diabetes mellitus at high cardiovascular risk. In this post hoc analysis of LEADER, we evaluated the effects of liraglutide stratified by a number of atherosclerotic vascular territories (coronary, cerebrovascular, and peripheral).

LEADER (ClinicalTrials.gov, NCT01179048) was a randomized trial of liraglutide (1.8 mg or maximum tolerated dose) versus placebo in 9340 patients with type 2 diabetes mellitus and high cardiovascular risk (median follow-up, 3.8 years).[5] The primary outcome was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (major adverse cardiovascular events [MACE]). The key secondary expanded outcome (expanded MACE) also included hospitalization for unstable angina, coronary revascularization, or hospitalization for heart failure.

The ethics committee or institutional review board at each participating center approved the trial protocol. Patients provided informed consent. Cardiovascular outcomes were prospectively adjudicated by an independent, blinded event adjudication committee. Atherosclerotic vascular territories included coronary (myocardial infarction, ≥50% coronary artery stenosis, percutaneous coronary intervention or coronary artery bypass graft surgery, angina pectoris, or asymptomatic ischemia), cerebrovascular (stroke, transient ischemic attack, ≥50% intracranial or carotid artery stenosis), and peripheral (≥50% peripheral artery stenosis) arteries. Information was extracted from patients' baseline medical history. Risk groups were determined by number of vascular territories involved: polyvascular disease as ≥2, single vascular disease as 1, and a group with no documented atherosclerotic cardiovascular disease (ASCVD).

The hazard ratios (HRs) comparing risk groups were calculated using a Cox proportional hazards model with treatment and risk group as factors. The treatment effect of liraglutide versus placebo within risk groups was estimated by using the Cox proportional hazards regression model with treatment, risk group, and the interaction of both as factors.

In LEADER, 6775 patients (72.5%) had documented ASCVD. In patients with ASCVD, 1536 (23%) had a baseline history of polyvascular disease, and 5239 (77%) had single vascular disease. For the total population, the distribution of vascular territory involvement is shown in the Figure (A). In brief, 5364 patients (57.4%) had a history of coronary artery disease, 1968 (21.1%) had cerebrovascular disease, 1184 (12.7%) had peripheral artery disease, and 2565 (27.5%) had no documented ASCVD. At baseline, in patients with polyvascular disease versus single vascular disease, mean age±SD was higher (65.1±7.7 versus 63.5±7.3

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years), and more patients were male (68.8% versus 67.9%), were current or previous smokers (67.1% versus 60.1%), had an estimated glomerular filtration rate <60 mL·min^{-1}·1.73m^{-}2 (27.1% versus 19.0%), had history of heart failure (26.4% versus 16.5%), had history of myocardial infarction (47.2% versus 39.7%), had history of stroke (33.5% versus 10.0%), or had history of peripheral artery disease (47.1% versus 8.5%), and there was a higher frequency of cardiovascular medication use (95.6% versus 92.7% for antihypertensive therapy, 83.8% versus 79.2% for lipid-lowering therapy, and 79.7% versus 75.7% for antiplatelet therapy). Baseline hemoglobin A_{1c} was similar between groups.

Patients with polyvascular disease had a higher risk of cardiovascular outcomes than those with single vascular disease (MACE: HR, 1.52; 95% confidence interval [CI], 1.33–1.73; expanded MACE: HR, 1.45; 95% CI, 1.31–1.62; cardiovascular death: HR, 1.41; 95% CI, 1.13–1.75) (Figure [B and C]).

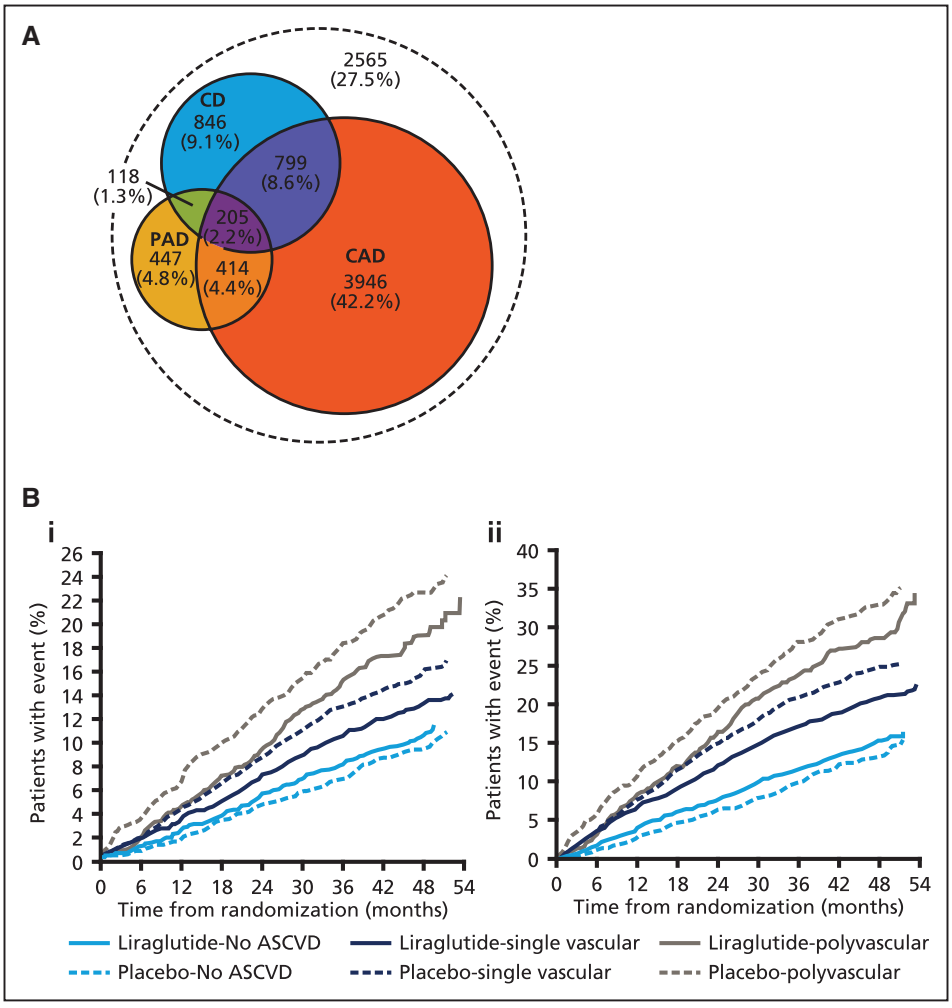

Figure. Analysis of LEADER data stratified by the number of atherosclerotic vascular territories (no ASCVD: no documented evidence of atherosclerotic disease in any of 3 vascular territories [coronary artery, cerebrovascular, or peripheral artery]; single vascular disease: atherosclerotic disease in 1 of the 3 vascular territories; polyvascular disease: atherosclerotic disease in ≥2 of the specified vascular territories).

A, Venn diagram of number (%) of patients according to number of vascular territories involved at baseline. **B,** Kaplan-Meier estimates (based on number of vascular territories involved at baseline) of time to first: primary MACE (composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) **(i)**, and expanded MACE (composite of the primary, with hospitalization for unstable angina, coronary revascularization, or hospitalization for heart failure also included) **(ii)**. **C,** Cardiovascular outcomes by number of vascular territories involved. Hazard ratios and 95% CIs are based on Cox regression analyses. Interaction *P* value is for test of homogeneity of treatment group difference among all 3 subgroups (no ASCVD, single vascular disease, and, polyvascular disease) with no adjustment for multiple tests. ASCVD indicates atherosclerotic cardiovascular disease; CAD, coronary artery disease; CD, cerebrovascular disease; CI, confidence interval; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MACE, major adverse cardiovascular event; and PAD, peripheral artery disease.

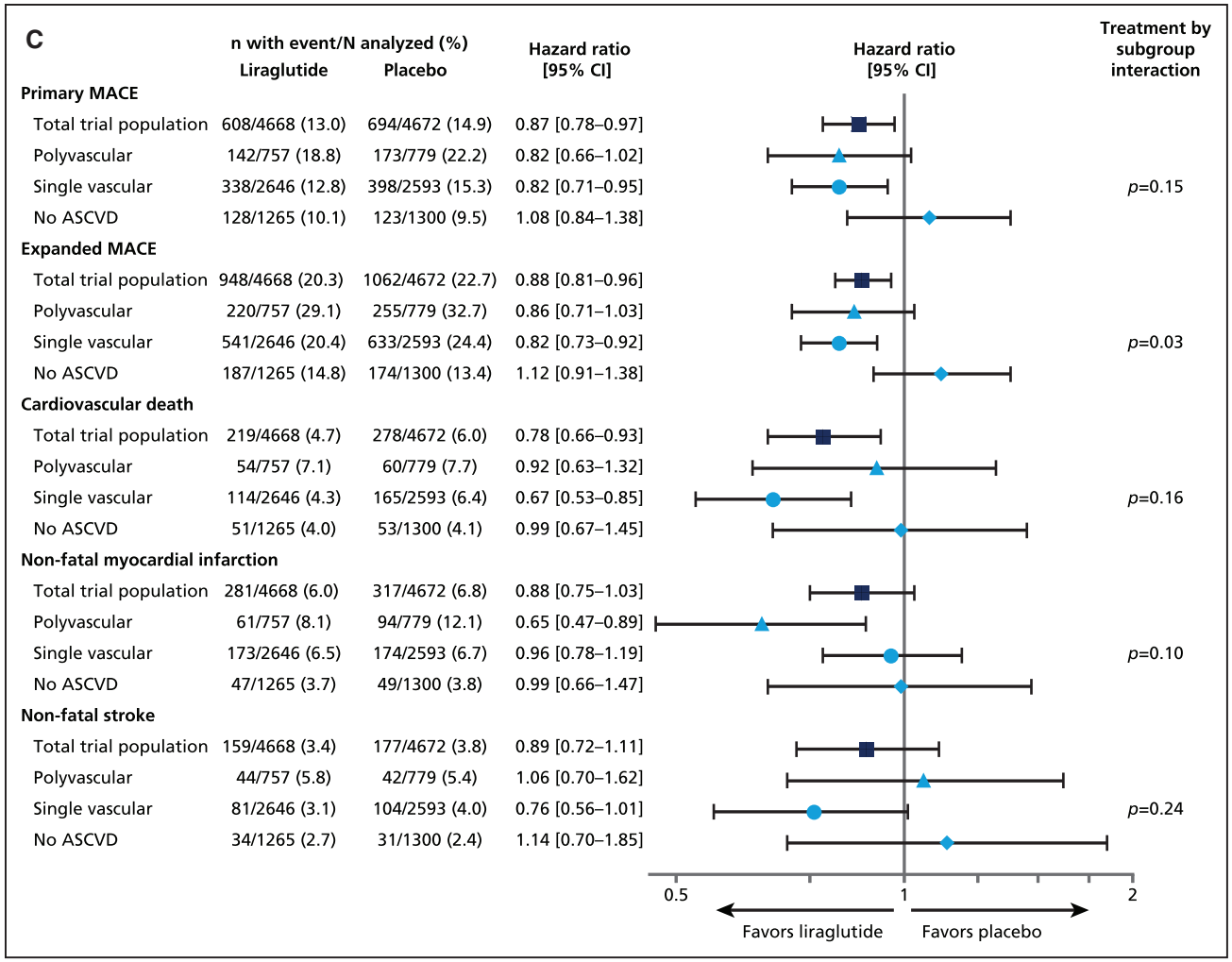

Figure Continued.

Liraglutide reduced MACE consistently in patients with polyvascular disease (HR, 0.82; 95% CI, 0.66–1.02) and with single vascular disease (HR, 0.82; 95% CI, 0.71–0.95). Results were similar for expanded MACE and cardiovascular death (Figure [C]). The risk reduction in MACE and expanded MACE was similar to that of the total trial population in LEADER (Figure [C]).[5] The corresponding data for nonfatal myocardial infarction and stroke are displayed in the Figure (C).

In patients without ASCVD at baseline, the HR for liraglutide versus placebo for MACE was 1.08 (95% CI, 0.84–1.38), with similar results for expanded MACE and cardiovascular death (Figure [C]). However, no significant interaction was found among risk groups, with the exception of expanded MACE ($P_{interaction}$=0.03), which could be a chance finding, because no adjustment for multiple testing was performed, or may suggest a difference in treatment effects across risk groups, driven by the group without ASCVD (Figure [C]). The reason for a neutral response in patients without ASCVD could be that the baseline risk was lower, and to establish any potential effect might require a longer treatment period or larger sample size. Nevertheless, patients with type 2 diabetes mellitus benefit from liraglutide treatment regarding glycemic control, potential weight reductions, and better blood pressure control.[5]

In patients with type 2 diabetes mellitus and documented ASCVD, the presence of polyvascular disease was associated with greater cardiovascular risk versus those with single vascular disease. Liraglutide consistently appeared to reduce major cardiovascular outcomes in both patients with polyvascular and single vascular disease.

ARTICLE INFORMATION

Data sharing: Data and analytic methods supporting this study's findings are available from the corresponding author on reasonable request.

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